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Background document for Session 7

Updating the WHO G6PD classification of variants and the International Classification of Diseases, 11th Revision (ICD-11)

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Background and rationale

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive disorder. It is the most common genetic abnormality affecting an estimated 400 million people worldwide. Although mostly asymptomatic, G6PD deficiency can lead to three clinical manifestations: (i) neonatal jaundice; (ii) acute haemolytic anaemia (AHA) triggered by infection, drugs (such as 8-aminoquinolines, e.g., primaquine/tafenoquine) or fava beans; and (iii) chronic non-spherocytic haemolytic disease (CNSHD). The gene encoding for G6PD is highly polymorphic, with over 300 variants and variable phenotypic expression in heterozygous females, depending on X-inactivation patterns. Variants are also associated with variable haemolytic risk, but this is not well characterized. G6PD deficiency is more common in malaria-endemic countries, and there is some evidence that the heterozygous state (females) confers protection from *Plasmodium* infection.

In the first-ever international WHO meeting on G6PD, held in December 1966, just 20 G6PD variants were described according to their biochemical characteristics, such as percentage (%) activity (measured by gold standard spectrophotometric assay), electrophoretic mobility, Km value, pH optimum and thermostability. This format served as the template for many publications over the next 20 years *(1).* The report from the meeting also recommended that the name of any G6PD variant be followed by an indicator of its activity, as follows: "(-) indicates 25% or less activity; (+/-) indicates 25–65% activity; (+) indicates normal activity (65–150%); (++) indicates greater than 150% activity". However, it was not until five years later that Yoshida, Beutler and Motulsky proposed the classification scheme we are familiar with today (Table 1), in an article published in the Bulletin of the World Health Organization *(2).* This classification scheme was accompanied by cautionary statements that have received less attention. These include: "*for purposes of convenience, the variants described in the accompanying table are somewhat arbitrarily divided into five classes*", and "*the distinction between these classes is not always clear*". Yoshida et al.'s classification quickly became known as the "WHO classification", even though the authors did not claim to have any mandate from WHO.

Table 1. Yoshida et al.'s proposed classification of G6PD, known as the "WHO Classification (Class I–V)", 1971

I. Activity <10% of normal, severe enzyme deficiency with chronic non-spherocytic haemolytic anaemia (CNSHA)

II. Activity <10% of normal, severe enzyme deficiency

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III. Activity 10–60% of normal, moderate to mild enzyme deficiency, intermittent acute haemolysis

IV. Very mild or no enzyme deficiency (60–100% of normal)

V. Increased enzyme activity (more than twice normal)

Yoshida et al.'s 1971 classification scheme was further reinforced when WHO assembled a Working Group on G6PD deficiency in 1985. The meeting report in the Bulletin of the World Health Organization (*3*) described 310 G6PD variants according to a slightly modified version[1] of the five classes in Table 1. Since 1986, when the full G6PD cDNA sequence was published, it has been possible to identify the individual mutations underlying many of the G6PD variants already known. Despite no formal WHO recommendation for change, over the past 30 years, some reports of new variants have provided both biochemical characterization and the identity of the underlying mutation(s). There has been a gradual shift from biochemical analysis to mutation analysis. However, biochemical data are important because they explain how the enzyme operates, which, in turn, influences response to oxidative stress.

In addition, technical consultations to inform the performance requirements for G6PD point-of-care tests to guide treatment with primaquine and tafenoquine have redefined 'normal' G6PD activity to be either >70% or >80% of normal *(4,5)*. No single additional case of G6PD *Hektoen* with activity >150% has ever been described, and some forms of CNSHA may have G6PD activity >10%. Most crucially, the cut-off of 10% activity that separates class II from class III was from its inception completely arbitrary, and a large number of G6PD variants currently classified as class II and class III have the same clinical manifestations. Furthermore, although certain variants that are currently in class II (e.g., G6PD Mediterranean), on average, yield more severe clinical manifestations than certain class III variants (e.g., G6PD A-), there is extensive overlap, and AHA can be severe or even life-threatening with any class II or class III variant. Finally, many variants have been placed into class II or class III based on a single measurement in a single person. Consensus is therefore needed on the process for determining the activity of a specific variant, e.g., number of patients, number of repeats. For these reasons, we propose that a Technical Consultation be held to revise the G6PD classification scheme and simultaneously incorporate these findings into a proposal to modify ICD-11[2]. ICD-11 currently only classifies G6PD deficiency under haemolytic anaemias, specifically as haemolytic anaemia due to G6PD deficiency (code: 3A10.00[3]). The current version of ICD-11 (04/19) will be updated in February 2020. Therefore, there is some urgency to submit a proposal to expand upon this classification so as to better reflect the occurrence of this condition, as well as the severity and range of clinical manifestations.

Why should the Global Malaria Programme (GMP) lead this effort?

In the malaria treatment guidelines *(6)*, WHO recommends that G6PD status be known prior to administration of primaquine. Therefore, scale-up of safe and effective radical cure for *P. vivax* is dependent upon the corresponding availability of quality, point-of-care G6PD testing and expansion of our knowledge on the haemolytic risk of various G6PD variants. These efforts should be

[1] Class I – associated with chronic non-spherocytic haemolytic anaemia (CNSHA). Class II – severely deficient: less than 10% residual activity. Class III – moderately deficient: 10–60% residual activity. Class IV – normal activity: 60–150%. Class V – increased activity.

[2] https://icd.who.int/en/

[3] ICD-11: 3A10.00 – Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common hereditary erythrocyte enzyme deficiency that can manifest with severe neonatal jaundice which can lead to serious neurological consequences, or, most often, with acute haemolytic anaemia following ingestion of certain foods (fava beans), common drugs (some antimalaria drugs, sulphamides, analgesics), or in the course of an infection, in otherwise asymptomatic individuals.

underpinned by updated nomenclature (also included in ICD-11) that can inform future monitoring of prevalence and clinical manifestations, and product development.

Over the past year, GMP, Prevention, Diagnosis and Treatment unit staff have attempted to identify the relevant departments/units of WHO responsible for guidance on G6PD. The Hereditary Diseases Programme/Human Genetics Programme that convened the consultations in the 1980s no longer exists, and G6PD deficiency seems to have been somewhat orphaned during the reorganizations over the past decades. Fortunately, the WHO Genomics Initiative, now hosted by the WHO Department of Service Delivery and Safety, convened an expert meeting in April 2019 on genomics and genetic disorders. The goals of the meeting were to set priority areas of work in low- and middle-income countries and develop a roadmap on genetics and genomics. Revising the current G6PD classification scheme was identified as a priority to take forward. Subsequent internal discussions with the ICD team revealed that G6PD is also under-represented in the current version, but that new modifications to the ICD architecture will enable a much more detailed categorization. Thus, the revisions to both the classification and ICD catalogue could be accomplished in parallel. The WHO Department of Service Delivery and Safety proposed that GMP coordinate the consultations required to achieve these revised schemes, as the results will immediately impact our work towards establishing policy and product specifications for point-of-care G6PD tests to guide use of 8-aminoquinolines for radical cure of *P. vivax.*

Objectives

i) Revise the most widely used classification of G6PD variants.

ii) Discuss requirements for defining new variants.

iii) Propose new categorization of G6PD for ICD-11, including classification of G6PD variants and clinical manifestations.

References

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